CLAIMS

1. A soluble derivative of a soluble polypeptide, said derivative comprising two or more heterologous membrane binding elements with low membrane affinity covalently associated with the polypeptide which elements are capable of interacting, independently and with thermodynamic additivity, with components of cellular or artificial membranes exposed to extracellular fluids.

2. A derivative according to claim 1 wherein each membrane binding element with low membrane affinityhas a dissociation constant 1μM-1mM.

3. A derivative according to claim 1 or 2 wherein each membrane binding element has a size <5kDa.

4. A derivative according to any preceding claim which incorporates sufficient elements with low affinities for membrane components to result in a 0.01 - 10nM dissociation constant affinity for specific membranes.

5. A derivative according to any preceding claim which has a solubility in pharmaceutial formulation media >100μg/ml.

6. A derivative according to any preceding claim wherein at least one element is hydrophilic.

7. A derivative according to any preceding claim which comprises two to eight membrane binding elements.

8. A derivative according to any preceding claim wherein the membrane binding elements are selected from: fatty acid derivatives; basic amino acid sequences; ligands of known integral membrane proteins; sequences derived from the complementarity-determining region of monoclonal antibodies raised against epitopes of membrane proteins; and membrane binding sequences identified through screening of random chemical or peptide libraries.

9. A derivative according to claim 8 wherein a membrane binding element is a fatty acid derivative selected from aliphatic acyl groups with about 8 to 18 methylene units, [illegible] aliphatic amines and thiols, steroid and farnesyl derivatives

22. A soluble derivative according to claim 20 or 21 selected from SEQ ID NOs: 8, 31, 9, 10, 11, 12, 13, 17, 24 and 36.

23. A soluble derivative according to any of claims 1 to 17 wherein the soluble polypeptide is a thrombolytic agent.

24. A soluble derivative according to claim 23 selected from SEQ ID NOs: 21 and 22.

25. A process for preparing a derivative according to claim 1 which process comprises expressing DNA encoding the polypeptide portion of said derivative in a recombinant host cell and recovering the product and thereafter post translationally modifying the polypeptide to chemically introduce membrane binding elements.

26. A polypeptide portion of a derivative according to claim 1, comprising the soluble peptide linked by a peptide bond to one peptidic membrane binding element

27. A soluble polypeptide including a C-terminal cysteine.

28. The polypeptide of SEQ ID NO: 7, 23, 33, 6 or 14.

29. A DNA polymer encoding the polypeptide portion of claim 26, 27 or 28.

30. A replicable expression vector capable, in a host cell, of expressing the DNA polymer of claim 29.

31. A host cell transformed with a replicable expression vector of claim 30.

32. A peptide membrane binding element with low membrane affinity comprising one or more derivatisations selected from:
a terminal cysteine residue optionally activated at the thiol group;
an N-haloacetyl group (where halo signifies chlorine, bromine or iodine) located at the N-terminus of the the peptide or at an ε-amino group of a lysine residue;
an amide group at the C-terminus;

33. A peptidic membrane binding element derivatised according to claim 32 wherein the peptide has the amino sequence of a peptide defined in claim 11 or 12 and a fatty acid N-acyl group of 8 to 18 methylene units at the N-terminus or at an ε-amino group of a lysine residue of the peptide.

34. A peptidic membrane binding element derivatised according to claim 32 or 33 selected from SEQ ID Nos: 27, 28, 29 and 30.

35. A C_{10-20} fatty acyl derivative of an aminoC_{2-6}alkane thiol (optionally C-substituted).

36. A compound according to claim 35 selected from N-(2-myristoyl) aminoethanethiol nd N-myristoyl L-cysteine.

37. A pharmaceutical composition comprising a derivative according to any of claims 1 to 24 in combination with a pharmaceutically acceptable carrier.

38. A derivative according to any of claims 1 to 24 for use as a medicament.

39. A method of treatment of disorders amenable to treatment by a soluble peptide which comprises administering a soluble derivative of said soluble peptide according to any of claims 1 to 24.

40. The use of a derivative according to any of claims 1 to 24 for the preparation of a medicament for treatment of disorders amenable to treatment by the soluble peptide.

41. A pharmaceutical composition for treating a disease or disorder associated with inflammation or inappropriate complement activation comprising a therapeutically effective amount of a derivative according to claim 19 and a pharmaceutically acceptable carrier or excipient.

42. A method of treating a disease or disorder associated with inflammation or inappropriate complement activation comprising administering to a subject in need of such treatment a therapeutically effective amount of a derivative according to claim 19.

43. The use of a derivative of claim 19 in the manufacture of a medicament for the treatment of a disease or disorder associated with inflammation or inappropriate complement activation.

44. A pharmaceutical composition for treating a disease or disorder associated with inflammation or inappropriate complement activation comprising a therapeutically effective amount of a soluble CR1 polypeptide derivative according to any of claims 20 to 22, and a pharmaceutically acceptable carrier or excipient.

45. A method of treating a disease or disorder associated with inflammation or inappropriate complement activation comprising administering to a subject in need of such treatment a therapeutically effective amount of a a soluble CR1 polypeptide derivative of any one of claims 20 to 22.

46. The use of a soluble CR1 polypeptide derivative of any one of claims 20 to 22 in the manufacture of a medicament for the treatment of a disease or disorder associated with inflammation or inappropriate complement activation.

47. A pharmaceutical composition for treating thrombotic disorders comprising a therapeutically effective amount of a derivative according to claim 23 or 24 and a pharmaceutically acceptable carrier or excipient.

48. A method of treating thrombotic disorders comprising administering to a subject in need of such treatment a therapeutically effective amount of a derivative according to claim 23 or 24.

49. The use of a derivative according to claim 23 or 24 in the manufacture of a medicament for the treatment of thrombotic disorders.

CLAIMS

1. A soluble derivative of a soluble polypeptide, said derivative comprising two or more heterologous membrane binding elements with low membrane affinity covalently associated with the polypeptide, which elements are not all identical and are capable of interacting, independently and with thermodynamic additivity, with components of cellular or artificial membranes exposed to extracellular fluids.

2. A derivative according to claim 1 wherein each membrane binding element with low membrane affinity has a dissociation constant 1μM-1mM.

3. A derivative according to claim 1 or 2 wherein each membrane binding element has a size <5kDa.

4. A derivative according to any preceding claim which incorporates sufficient elements with low affinities for membrane components to result in a 0.01 - 10nM dissociation constant affinity for specific membranes.

5. A derivative according to any preceding claim which has a solubility in pharmaceutial formulation media >100μg/ml.

6. A derivative according to any preceding claim wherein at least one element is hydrophilic.

7. A derivative according to any preceding claim which comprises two to eight membrane binding elements.

8. A derivative according to any preceding claim wherein the membrane binding elements are selected from: fatty acid derivatives; basic amino acid sequences; ligands of known integral membrane proteins; sequences derived from the complementarity-determining region of monoclonal antibodies raised against epitopes of membrane proteins; and membrane binding sequences identified through screening of random chemical or peptide libraries.

9. A derivative according to claim 8 wherein a membrane binding element is a fatty

10. A derivative according to claim 8 ~~or 9~~ wherein a membrane binding element is a basic aminoacid sequence including (Lys)n where n is from 3 to 10.

11. A derivative according to claim 10 wherein the amino acid sequence is selected from:

i) DGPKKKKKKSPSKSSG
ii) GSSKSPSKKKKKKPGD
iii) SPSNETPKKKKKRFSFKKSG
iv) DGPKKKKKKSPSKSSK
v) SKDGKKKKKKSKTK
(N-terminus on left)

12. A derivative according to ~~any of claims 8 to 10~~ wherein a membrane binding element is a ligand of a known integral membrane protein selected from GRGDSP, DGPSEILRGDFSS, GNEQSFRVDLRTLLRYA, GFRILLLKV, SAAPSSGFRILLLKV and AAPSVIGFRILLLKVAG or the carbohydrate ligand Sialyl Lewis^x.

13. A derivative according to ~~any preceding claim~~ wherein the soluble polypeptide is selected from IL-4 Y124D mutein, prourokinase, streptokinase, tissue-type plasminogen activator, reteplase, leptin, complement inhibitors selected from complement regulatory proteins and hybrids or muteins thereof, scFv antibody against cytokines, Protein C, antibodies against CD4, B7/CD28, CD3/TCR or CD11b(CR3) and Interferon-β and derivatives.

14. A derivative according to ~~any preceding claim~~ which has the following structure:

$$\mathbf{[P]\text{-}\{L\text{-}[W]\}_n\text{-}X}$$

in which:
P is the soluble polypeptide,
each **L** is independently a flexible linker group,
each **W** is independently a peptidic membrane binding element,
n is an integer of 1 or more and
X is a peptidic or non-peptidic membrane-binding entity which may be covalently linked to any **W**.

15. A derivative according to claim 14 wherein peptidic membrane binding elements

another and to the soluble peptide by linker groups which are selected from: hydrophilic and/or flexible aminoacid sequences of 4 to 20 aminoacids; linear hydrophilic synthetic polymers; and chemical bridging groups.

16. A derivative according to claim 14 ~~or 15~~ wherein the chemical bridging groups are of formula (I):

-A-R-B- (I)

in which each of A and B, which may be the same or different, represents -CO-, -C(=NH_2^+)-, maleimido, -S- or a bond and R is a bond or a linking group containing one or more -(CH_2)- or meta-, ortho- or para- disubstituted phenyl units optionally together with a hydrophilic portion.

17. A derivative according to claim 16 wherein R is selected from -$(CH_2)_r$-, -$(CH_2)_p$-S-S-$(CH_2)_q$- and -$(CH_2)_p$-CH(OH)-CH(OH)-$(CH_2)_q$-, in which r is an integer of at least 2, and p and q are independently integers of at least 2, or $(CH_2)_2CONH(CH_2)_nNH$-(4-phenyl) where n is an integer of 3 to 8.

18. A soluble derivative according to claim 1 of SEQ ID NO: 32.

19. A soluble derivative according to ~~any~~ of claims 1 to ~~17~~ wherein the soluble polypeptide is a soluble complement inhibitor.

20. A soluble derivative according to claim 19 wherein the soluble polypeptide is a soluble CR1 polypeptide fragment.

21. A soluble derivative according to claim 20 wherein the soluble CR1 polypeptide consists of residues 1-196 of CR1 and with an N-terminal methionine and the derivative comprises a myristoyl group and one or more polypeptides sequence selected from

DGPKKKKKKSPSKSSGC
GSSKSPSKKKKKKPGDC
CDGPKKKKKKSPSKSSK
SKDGKKKKKKSKTKC
CSAAPSSGFRILLLKV
AAPSVIGFRILLLKVAGC
and
DGPSFIL RGDFSSC

22. A soluble derivative according to claim 20 or 21 selected from SEQ ID NOs: 8, 31, 9, 10, 11, 12, 13, 17, 24 and 36.

23. A soluble derivative according to ~~any~~ of claims 1 to 17 wherein the soluble polypeptide is a thrombolytic agent.

24. A soluble derivative according to claim 23 selected from SEQ ID NOs: 21 and 22.

25. A process for preparing a derivative according to claim 1 which process comprises expressing DNA encoding the polypeptide portion of said derivative in a recombinant host cell and recovering the product and thereafter post translationally modifying the polypeptide to chemically introduce membrane binding elements.

26. A polypeptide portion of a derivative according to claim 1, comprising the soluble peptide linked by a peptide bond to one peptidic membrane binding element, said element having low membrane affinity.

27. A soluble derivative of a soluble polypeptide according to claim 1 ~~or a polypeptide portion of a derivative according to claim 26~~, wherein the soluble polypeptide includes a C-terminal cysteine.

28. The polypeptide of SEQ ID NO: 7, 23, 33, 6 or 14.

29. A DNA polymer encoding the polypeptide portion of claim 26, 27 or 28.

30. A replicable expression vector capable, in a host cell, of expressing the DNA polymer of claim 29.

31. A host cell transformed with a replicable expression vector of claim 30.

32. A peptide membrane binding element with low membrane affinity comprising one or more derivatisations selected from:
a terminal cysteine residue optionally activated at the thiol group;

an amide group at the C-terminus;
an N-terminal blocking group; and
a fatty acid N-acyl group at the N-terminus or at an amino group of a lysine residue

33. A peptidic membrane binding element derivatised according to claim 32 wherein the peptide has the amino sequence of a peptide defined in claim 11 or 12 and a fatty acid N-acyl group of 8 to 18 methylene units at the N-terminus or at an ε-amino group of a lysine residue of the peptide.

34. A peptidic membrane binding element derivatised according to claim 32 or 33 selected from SEQ ID Nos: 27, 28, 29 and 30.

35. A soluble derivative of a soluble polypeptide according to claim 1 ~~or a polypeptide portion of a derivative according to claim 26~~, wherein at least one membrane binding element with low membrane affinity is a C_{8-20} fatty acyl derivative of an aminoC_{2-6}alkane thiol (optionally C-substituted).

36. A compound according to claim 35 selected from N-(2-myristoyl) aminoethanethiol nd N-myristoyl L-cysteine.

37. A pharmaceutical composition comprising a derivative according to any of claims 1 to 24 in combination with a pharmaceutically acceptable carrier.

38. A derivative according to any of claims 1 to 24 for use as a medicament.

39. A method of treatment of disorders amenable to treatment by a soluble peptide which comprises administering a soluble derivative of said soluble peptide according to any of claims 1 to 24.

40. The use of a derivative according to any of claims 1 to 24 for the preparation of a medicament for treatment of disorders amenable to treatment by the soluble peptide.

41. A pharmaceutical composition for treating a disease or disorder associated with inflammation or inappropriate complement activation comprising a therapeutically effective amount of a derivative according to claim 19 and a pharmaceutically acceptable carrier or excipient.

[illegible] treatment a therapeutically effective amount of a derivative according to claim [illegible]